

Guideline 1-23-A

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario) in Collaboration with the American Society of Clinical Oncology (ASCO)

Management of the axilla in early-stage breast cancer

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An assessment conducted in December 2023 deferred the review of Guideline 1-23-A. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

Guideline 1-23-A is comprised of 5 sections. You can access the summary and full report here:

<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/69736>

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- Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2014;32:1365-83.
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Management of the axilla in early-stage breast cancer

Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVES

General Objectives:

To provide recommendations on the best strategies for the management, and on the best timing and treatment (surgical and radio-therapeutic) of the axilla in early-stage breast cancer.

Specific Objectives:

Specific objectives are listed before each recommendation.

TARGET POPULATION

These recommendations apply to patients with early-stage breast cancer (i.e., stages I, IIA, IIB; and prognostic groups T1, T2, N0, N1mi, N1, M0; and primary tumour size ≤ 5 cm).

INTENDED USERS

This guideline is targeted for:

1. General surgeons involved in the staging of early breast cancer and management of the axilla.
2. Radiation oncologists involved in the radiation treatment of patients with early-stage breast cancer.
3. Medical oncologists involved in the systemic treatment of patients with early-stage breast cancer.
4. Other clinicians involved in the management of women with early-stage breast cancer (e.g., pathologists, radiologists, oncology nurses, genetic counselors).

DEFINITIONS:

- 1) A **patient-centred approach** involves considering each patient on a case-by-case basis, discussing pros and cons of various options with the patient, in light of her or his circumstances, values and preferences, and using a shared decision-making process for choosing treatment.
- 2) **Clinical versus pathological positivity:** We define a clinically positive axilla as clinically palpable disease where the determination is made by physical examination only. Pathological positivity means that metastatic cells are identified in the axillary nodes at histopathology, conducted either by fine needle or core biopsy at diagnosis, or postoperatively as a result of sentinel lymph node biopsy (SLNB), or axillary lymph node dissection (ALND). In this document, when we describe patients as positive or negative, we mean that they are pathologically positive or negative, unless otherwise specified. We do not consider lymph nodes to be pathologically positive if they only contain isolated tumour cells.

- 3) **Radiotherapy of the axilla:** Axillary radiation delivered by standard 2-field tangents to the breast/chest wall that will cover the level 1 and 2 lymph nodes in the axilla, without additional fields to the axilla as is utilized in loco-regional nodal radiation.
- 4) **Early-stage breast cancer** is defined by the US National Cancer Institute as breast cancer that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ (DCIS) and stages I, IIA, IIB, and IIIA breast cancers (<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/early-stage-breast-cancer>). For this report we excluded women with DCIS because they are stage 0 and should not require staging since the cells, by definition, do not spread beyond the basement membrane of the lactiferous duct. We did not include women with stage IIIA because stage III is considered locally advanced and it is covered by our Evidence-Based Series #1-19: “Loco-regional Therapy of Locally Advanced Breast Cancer” [1] available at: <https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=334821>.
- 5) **Cancer staging** definitions, see the American Joint Committee on Cancer (AJCC) manual, 8th edition, last updated 05 June, 2018, available at: <https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%20Cancer%20Staging%20Form%20Supplement.pdf> [2]
- 6) Patients with negative nodes and with high-risk features are patients younger than 50 years of age, or premenopausal, or with primary tumour measuring ≥ 5 cm, or ≥ 2 cm with < 10 axillary nodes removed and at least one of: grade III histologic categorization, estrogen-receptor negativity, or lymphovascular invasion (e.g., with triple-negative breast cancer).
- 7) In this document, loco-regional radiotherapy refers to whole breast, chest wall, and regional nodal basins irradiation.

SPECIFIC OBJECTIVES AND RECOMMENDATIONS

For all recommendations we recommend a patient-centred approach.

An algorithm for the management of the axilla in patients with early-stage breast cancer is presented in Figure 1.

Specific objective 1: To determine which patients with early-stage breast cancer require axillary staging.

Recommendation 1
<ul style="list-style-type: none"> • For patients ≥ 70 years of age with clinically node-negative (T1N0) early-stage invasive breast cancer which is hormone receptor positive and HER2 negative, SLNB is not required. This is supported by the Choosing Wisely statement released on July 12, 2016, and updated on June 20, 2019 by the Society of Surgical Oncology (SSO) available at: http://www.choosingwisely.org/clinician-lists/sso-sentinel-node-biopsy-in-node-negative-women-70-and-over/ that stated: “Don’t routinely use sentinel node biopsy in clinically node negative women ≥ 70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer” if they will be treated with hormonal therapy. If omission of SLNB is considered, a consultation with a medical oncologist can be considered before surgery to discuss hormonal therapy. • For patients < 70 years of age without significant competing comorbidities, SLNB should be considered for axillary staging of early-stage breast cancer.
Qualifying Statements for Recommendation 1
<ul style="list-style-type: none"> • The information acquired from SLNB would be helpful in guiding adjuvant treatment decision making. • Patients should be evaluated on a case-by-case basis to ensure appropriate patient-centred decision making.

- Patients who are clinically node negative on physical examination, but are found to be sonographically abnormal on imaging with or without confirmatory biopsy can be offered SLNB as first-line axillary staging.

Specific objective 2: To determine whether any further axillary treatment is indicated for women with early-stage breast cancer who did not receive neoadjuvant chemotherapy (NAC) and are sentinel lymph node negative at diagnosis.

Recommendation 2

Clinicians should not recommend ALND for women with early-stage breast cancer who do not have nodal metastases (endorsed from Recommendation 1 of the American Society of Clinical Oncology [ASCO] 2017 update guideline [3,4]).

In some selected patients (e.g., patients with medially or centrally located tumours or with high-risk features), and using a patient-centred approach, it is reasonable to offer the option of loco-regional radiation to include at least the supraclavicular and ipsilateral internal mammary lymph nodes in addition to the breast and/or chest wall (see Qualifying Statement).

For the majority of patients (i.e., node-negative patients whose tumours are not medial/central in location, and who do not have other high-risk features), however, we cannot recommend loco-regional node irradiation. Risk-benefit discussion should be undertaken on a case-by-case basis for these patients (see Qualifying Statement).

Qualifying Statements for Recommendation 2

Surgical interventions:

- SLNB is currently the standard of practice for this population.
- The evidence regarding the omission of ALND upon which this recommendation is based (see key evidence for Recommendation 2) did not include patients who: had a history of another cancer, had a multicentric breast cancer, had a prior ipsilateral breast cancer surgery or prior ipsilateral axillary surgery, were <18 or >80 years of age, were pregnant or lactating, were allergic to blue dye or radioisotope, had evidence of metastatic disease, had tumours >3 cm in diameter, suffered from chronic life-threatening diseases possibly preventing the use of adjuvant therapy, had stage T0 tumours (e.g., ductal carcinoma in situ), had multifocal tumours, and received previous NAC. For these patients, decisions regarding ALND should be made after discussion between the patient and clinicians on a case-by-case basis, depending on the invasive component of the lesion, other clinical circumstances and patient preferences.

Radiotherapy interventions

- Patients with central or medially located tumours may modestly benefit (<5%) from loco-regional irradiation compared with whole breast only (post lumpectomy) or no post-operative radiation (post-mastectomy) in terms of disease-free survival (DFS), distant DFS, and loco-regional relapse, but not in terms of overall survival (OS).
- Post-mastectomy patients with node-negative, triple-negative breast cancer who receive chemotherapy may benefit in DFS and OS from chest wall radiotherapy compared with no radiotherapy.
- A radiotherapy dose fractionation schedule of 50 Gy in 25 fractions over five weeks is the current standard schedule used in the relevant clinical trials; however, we recognize that there are other regimens now considered clinically appropriate and/or equivalent to this traditional fractionation.

Specific objective 3: To determine which axillary strategy is indicated for women with early-stage breast cancer who did not receive NAC and are pathologically sentinel lymph node-positive at diagnosis (after a clinically node-negative presentation).

Recommendation 3
<p>A) No further axillary surgery beyond SLNB compared with ALND Clinicians should not recommend ALND for women with early-stage breast cancer who have one or two sentinel lymph node metastases and will receive breast-conserving surgery with conventionally fractionated whole-breast radiotherapy (endorsed from ASCO 2017 guideline [3,4], Recommendation 2.1).</p> <p>B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no radiation to the loco-regional lymph nodes. It is reasonable to offer the option of treating the axilla with radiotherapy in addition to breast or chest wall irradiation following surgery, particularly in patients with medial/central tumours, and in patients with high-risk features. Discussion of pros and cons with patients needs to occur, and decisions should be made on a case-by-case basis.</p> <p>C) Radiotherapy to the axilla compared with further surgery (ALND) We recommend radiotherapy of the axilla in lieu of ALND in patients who are clinically node negative and pathologically sentinel lymph node positive with tumours of up to 5 cm, and unifocal or multifocal disease restricted to one quadrant.</p> <p>In patients who receive breast-conserving surgery, we recommend no ALND if one or two sentinel lymph nodes are positive. Loco-regional radiation is a reasonable option, especially when there are high-risk features as in (B) above.</p> <p>ALND and loco-regional radiation to the axilla is recommended if ≥ 3 sentinel lymph nodes are positive.</p> <p>In patients who undergo mastectomy and have one to two positive nodes, post-mastectomy radiation (PMRT) to the chest wall and the axilla is recommended and ALND can be safely omitted. In patients declining PMRT (i.e., patients with immediate reconstruction), either radiation to the axilla without the chest wall or completion ALND can be considered. In patients who undergo mastectomy and have ≥ 3 positive nodes, ALND followed by loco-regional radiation can be considered.</p> <p>D) Radiotherapy compared with no treatment In patients with unilateral invasive cancer of small size (i.e., T1a), favourable tumour features (e.g., estrogen receptor-positive undergoing hormonal therapy), clear margins, and one to three positive nodes, treated with chemotherapy or hormonal therapy, clinicians might offer the option of omitting radiotherapy of the regional nodes.</p>
Qualifying Statements for Recommendation 3
<p>A) No further axillary surgery beyond SLNB compared with ALND The evidence upon which this recommendation is based did not include patients who: Were pregnant or breastfeeding, had a history of another malignancy in the previous five years, had bilateral breast cancer, had multicentric disease, had ≥ 3 or more positive sentinel lymph nodes, had a concomitant malignancy, were previously treated with systemic therapy for</p>

breast cancer, had chemoprevention in the preceding year, had distant metastases or macrometastatic disease, had palpable axillary nodes, were <18 or >75 years old

For these patients, as well as for patients who are treated with mastectomy, decisions regarding completion of ALND should be made after discussion between the patient and clinicians on a case-by-case basis depending on the invasive component of the lesion, other clinical circumstances, and patient preferences, taking into account the limited data specific to mastectomy and considering that these recommendations represent an extrapolation, based on expert opinion, from trials designed for patients undergoing breast-conserving surgery.

For a detailed description of patients who were included in the studies upon which this recommendation is based, see Appendix 7, Tables A to D.

The management of the axilla for patients with four or more positive lymph nodes (N2, N3 disease) falls outside the scope of this guideline. Please refer to Cancer Care Ontario PEBC guideline 19-1 guideline: “Loco-regional therapy of locally advanced breast cancer (LABC)” [1]. For exactly three positive lymph node there is not enough evidence to make a recommendation; therefore, we recommend proceeding with ALND and considering regional radiation.

B) Radiotherapy of the axilla (loco-regional node irradiation) compared with no irradiation to the loco-regional lymph nodes.

Patients with estrogen- and progesterone-negative receptor status may have a more favourable DFS when treated with loco-regional irradiation in addition to surgery.

C) Radiotherapy to the axilla compared with further surgery (ALND)

The ongoing MA39 (NCT00005957) study addresses the incremental benefit of loco-regional nodal irradiation of the axilla in lower-risk, node-positive patients. At this time, no studies comparing SLNB alone without loco-regional node irradiation have been identified in the mastectomy or lumpectomy setting.

D) Radiotherapy compared with no treatment

Patients 65 years of age or older may benefit less from the addition of radiotherapy. Receptor-negative patients may benefit more from radiotherapy treatment.

Specific objectives 4: to determine what axillary treatment is indicated and what is the best timing of treatment for women with early-stage breast cancer treated with NAC.

Recommendation 4

A) Initially node-negative patients

Patients who are initially clinically node negative on physical examination, and those who had clinically suspicious nodes on physical examination but deemed to be pathologically negative at fine needle aspiration/core needle biopsy, and have been treated with NAC, should have SLNB at the time of surgery as their axillary staging procedure.

B) Initially node-positive patients

1. For patients who were initially clinically and biopsy-proven node positive, and who remained clinically node positive after NAC we recommend ALND.
2. For patients who were initially clinically and biopsy-proven node positive, and became node negative after NAC, we recommend SLNB to restage the axilla. Restaging can be

achieved by placing a biopsy clip into the biopsied positive node at diagnosis and localizing it at surgery along with SLNB, or, in institutions where the use of biopsy clips for nodes is not available, by performing SLNB with dual tracer and excising at least three sentinel nodes in order to minimize the false negative rate and optimize accuracy of the procedure. At this time, we also recommend loco-regional radiation for these patients, regardless of pathologic status of sentinel lymph nodes.

3. Post-mastectomy patients who are node positive on surgical pathology after NAC can be offered PMRT after a completion ALND.
4. We recommend loco-regional nodal irradiation for post-mastectomy node-positive patients after NAC while awaiting data from ongoing trials (i.e., the MAC19 study).
5. We recommend loco-regional irradiation after ALND for patients clinically and biopsy-proven node positive at breast-conserving surgery who remain pathologically node positive after NAC.
6. Shared decision-making processes should be put in place while we await mature clinical trial data, to enable patient value-based decision making.

C) SLNB Timing: before or after NAC

We recommend against performing lymph node sampling twice, before and after NAC. We recommend that SLNB be performed after NAC and not before in clinically node-negative patients who will receive NAC.

Qualifying Statements for Recommendation 4

B) Initially clinically positive and biopsy proven node-positive patients

- To enable patient value-based decision making, shared decision making processes should be put in place, and a decision aid could be developed while we await mature clinical trial data.
- To date, the clinical standards of care for node-positive patients who fail to respond clinically in the axilla to NAC require maximal therapy to the axilla, which includes ALND followed by loco-regional nodal irradiation.

Specific objective 5: To determine which are the best methods for identifying sentinel nodes.

Recommendation 5

A) Single versus dual tracer

For patients having primary surgery, we recommend using a single sentinel node tracer (e.g., it is not necessary to add blue dye on a regular basis for SLNB if the radiocolloid signal successfully identifies the sentinel node(s) in the axilla).

In cases of non-identification, blue dye can be added. Screening for radiocolloid signal prior to incision is recommended, and, in cases of non-identification, blue dye can be added prior to making the incision.

In patients who receive NAC, we recommend either placing a biopsy clip into the positive node at diagnosis and localizing it at time of surgery, or using dual tracer (radiocolloid plus blue dye).

B) Ultrasound-guided (US-guided) staging versus standard guided (dye/isotope) staging

In clinically node-negative patients with early-stage breast cancer where the sentinel lymph node is likely to be negative (i.e., T1 and T2), preoperative axillary US staging is not recommended.

In patients with clinically palpable (i.e., clinically positive) lymph nodes, it is recommended that US-guided core biopsy of the axillary node be undertaken to prove pathological positivity. If patients are pathologically negative on image-guided lymph node biopsy, see Recommendation 2. If they are pathologically positive on image-guided lymph node biopsy, see Recommendation 3.

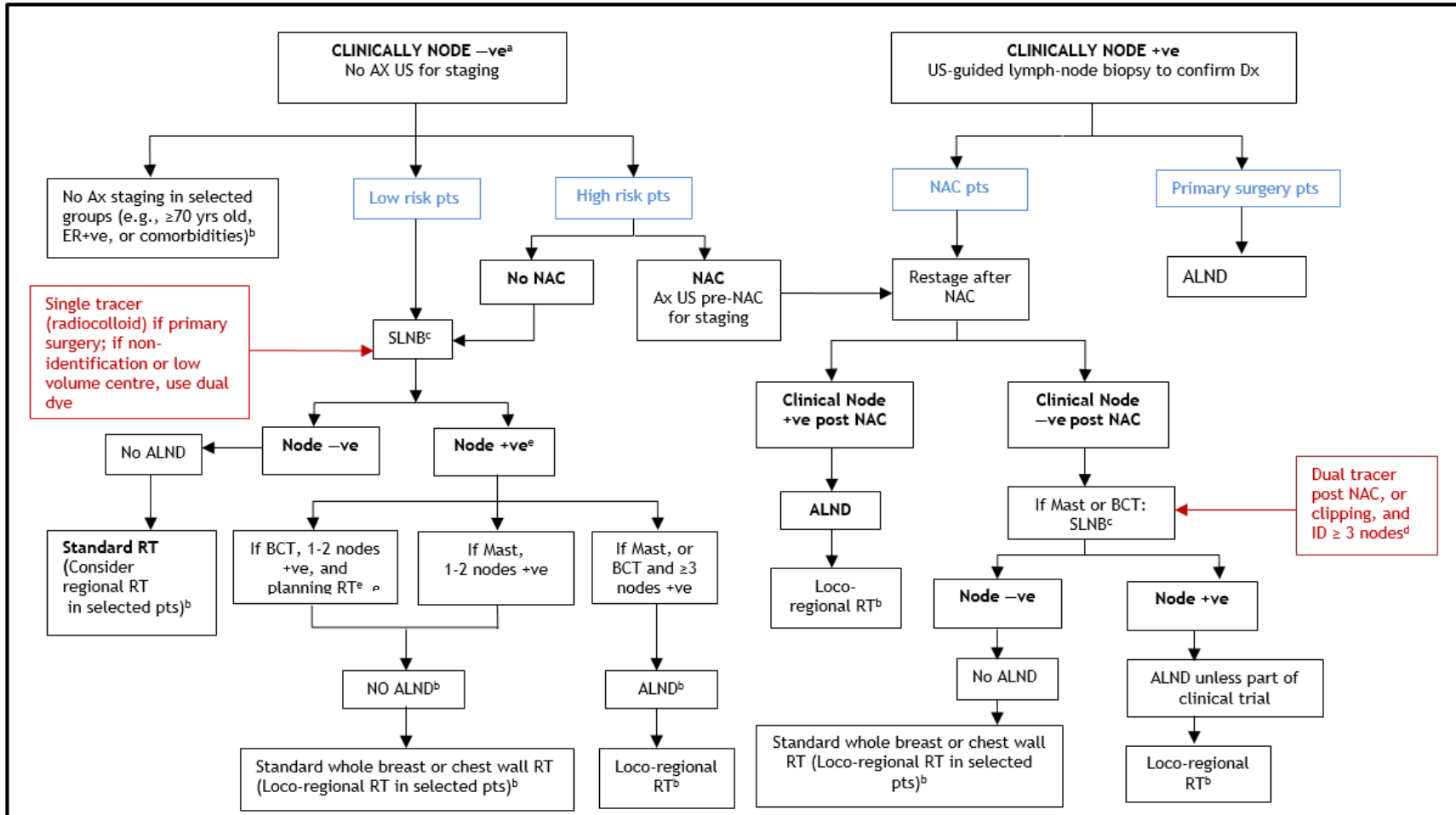
C) US staging versus surgical staging

We recommend that diagnostic staging by US only (i.e., not confirmed by a biopsy) not be used instead of standard SLNB staging.

Qualifying Statements for Recommendation 5

- A) Dual tracer should be used in settings where it is expected to be a learning curve for the operators performing the procedure (e.g. low volume centers, surgeons in training/post training).
- B) If a clip is used to identify a biopsied lymph node at diagnosis, the node containing the clip needs to be localized to make sure it is excised. If dual tracer is used, three or more sentinel nodes have to be identified. If three or more sentinel nodes are not identified in a patient who has had NAC according to standard sentinel lymph node techniques, an axillary dissection is recommended.

Figure 1-1. Algorithm for the management of the axilla in patients with early-stage (clinical stage T1,T2, N0,N1 [Stage I to Stage IIB]) breast cancer



a Refers to all patients with no palpable axillary nodes on physical examination, including those who may have had an ultrasound that was equivocal, abnormal, or even biopsy-proven positive.
 b Decision making should be made on a case-by-case basis, and include a patient centered approach, that is consider and discuss pros and cons of various options in light of patient’s specific circumstances, values and preferences.
 c Do not recommend SLNB before chemotherapy except in special circumstances after multidisciplinary discussion.
 d Evidence supports the use of dual localizing tracer (blue dye and radio-isotope) and harvesting ≥3 nodes or else do ALND to minimize false negative rate; any clipped positive nodes should be localized for surgery.
 e In rare circumstances (e.g., a small T1aN1) it is possible to avoid radiation (see Justification of Recommendation 3D)

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+ve = positive; -ve = negative; ALND = axillary lymph node dissection; Ax = axillary; BCT = breast conserving therapy; ER = estrogen receptor; HT = hormonal therapy; Mast = mastectomy; NAC = neo-adjuvant chemotherapy; pts = patients; RT = radiation treatment; SLNB = sentinel lymph node biopsy; US = ultrasound; yrs = years.